ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Editorial

Alpha-1 Antitrypsin: The Hypothesis of Inflammatory-Cocarcinogenic Process in Colorectal Carcinoma

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Received: October 30, 2017; **Published:** November 21, 2017

Alpha-1 antitrypsin (AT) is a circulating glycoprotein involved on anti-inflammatory processes in blood and tissues that modulates most inflammatory reactions occurring in human body, including the carcinogenic/cocarcinogenic process. In fact, AT deficiency is a hereditary condition that typically predisposes to premature onset of chronic obstructive pulmonary disease, liver cirrhosis, relapsing panniculitis, systemic vasculitis, and possibly a range of inflammatory and neoplastic diseases.

Colorectal carcinoma (CRC), a leading cause of cancer deaths worldwide, is mostly related to older age, male gender, high intake of fat, alcohol or red meat, obesity, smoking, and lack of physical activity, and only a small number of cases are due to inflammatory bowel disease or underlying genetic disorders, including familial adenomatous polyposis and hereditary non-polyposis colon cancer.

In the study of the relationship between AT and CRC, a case-control study were published in 2014 [1], in which a significantly higher serum concentrations of AT among colorectal cancer (CRC) than in healthy population ($p = 0.0001$), and a trend towards a higher frequency of allelic deficiency in CRC (21%) compared to healthy subjects (15%) were found. Following this hypothesis (that was reported more than 35 years ago, but still remains controversial), a state of the art of the literature was published in 2016 [2], in which a review for English language articles enlisted in the MEDLINE®/PubMED®, Embase, and Google Scholar databases was performed, applying the Oxford Centre for Evidence-Based Medicine (CEBM) guidelines. Five studies, representing 2625 patients with CRC and 2959 general population controls were included, and levels of evidence varied from CEBM level 3a ($n = 1$) to 3b ($n = 3$) and 4 ($n = 1$). The only three clinico-epidemiological studies carried out to date produced conflicting results. So, the level of evidence found on this relationship was very weak. Unfortunately, with the data obtained this hypothesis could not be rejected or approved.

In a mini-review of the current literature, a total of 18 papers have been found, and all of them addressed the hypothesis that AT could be a potential biomarker both in screening and diagnose in some kinds of carcinomas, including CRC. The level of evidence, in terms of evidence-based medicine, is high with respect to develop hepatocellular or bronchial carcinomas, in which the mechanism involved, would be an excess of neutrophil elastase that is not neutralized by AT, and that stimulates development, invasion and metastasis. This same mechanism would probably be shared by all other types of cancers, including CRC. Normal and cancer colonic cells secrete AT to neutralize elastase, in an attempt to maintain the protease-antiprotease balance. So, AT prevents the procathepsin B and proprotein convertase action, and reduces the production of TNF-α and IL-1a, preventing liver metastases. Other authors have related carcinogenesis to AT degradation by matrix metalloproteinases, resulting in production of COOH-terminal fragments, which increases tumor growth. Moreover, a mechanism of sustained autophagy triggered by AT was observed in colonic cells, which opposed apoptosis, and AT could have an anti-apoptotic property against non-malignant cells. But, the presence of AT in tumors, attributed to the tumor cells themselves, makes patients with AT expression in their tumors to have a worse prognosis.

Some authors have mentioned the total antioxidant status to be involved in the colonic cocarcinogenic process, in terms of the levels of lipid peroxidation products (malondialdehyde and 4-hydroxynonenal), the activity of cathepsin G, the intake of non-steroids anti-inflam-

matory drugs, or smoking. Khenjanta demonstrated a significant correlation with metastasis of cholangiocarcinoma, if low expression of Cytochrome P450 (CYP) enzymes were detected, and interestingly, oxidized alpha-1 antitrypsin (ox-A1AT), an oxidative stress marker, was significantly increased in CCA tissues in which CYP39A1 and RUNX2 were down regulated. A mechanism for the broad immune-regulatory properties of AT independent of its antiprotease activity, via peroxisome proliferator-activated receptors (PPAR)-dependent pathway has been provided recently. Finally, Yang published a significant association (as an etiologic link) between AT alleles and development of CRC with defective DNA mismatch repair in the development of MSI-H CRC.

In conclusion, data provided by the studies suggest that the presence of elevated serum levels of AT in patients with some types of carcinomas is related to an invasive growth of them. However, the low power of these data (in absence of epidemiologic studies, with conflicting data in some cases, or their small sample sizes in others) makes both the true value of this biomarker and its pathway in the development of CRC remain uncertain, so that more powerful studies are needed on this issue.

Bibliography

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Volume 4 Issue 3 November 2017